Chapter 8

Summary and General discussion

Summary

This thesis describes several potential risk factors for mortality due to cancer in the general population. We studied risk factors for mortality due to the four most common types of cancer, i.e. lung cancer, colorectal cancer, prostate cancer, and breast cancer, and mortality due to any cancer.

In **Chapter 2** the impact of baseline and lifetime smoking history on risk of mortality due to all-cause, and cause-specific mortality (i.e. mortality due to cardiovascular diseases (CVD), any cancer, lung, colorectal, prostate, and breast cancer) is described. Tobacco smoking is the primary preventable risk factor associated with mortality worldwide (1). Therefore, it is an important risk factor studied in this thesis. We showed that current smoking (light, moderate, and heavy cigarette smoking), and lifetime persistent smoking were associated with an increased risk of all-cause mortality, CVD and mortality due to any cancer, lung cancer compared to never smoking, the hazard ratios being highest for heavy smokers. A higher number of pack-years at baseline was associated with an increased risk of all-cause mortality, CVD and mortality to any cancer, lung cancer. Additionally, we assessed whether the association between smoking habits and mortality risk was different for males and females. We found significant interactions between smoking and sex on cause-specific mortality. The effects of persistent cigarette smoking on the risk of all-cause, CVD and lung cancer mortality were more pronounced in females, indicating a synergistic effect between smoking and sex. Another objective of this study was to assess the risk of pipe/cigar smoking for mortality. In line with previous findings described in the literatures, our results confirmed the associations of pipe and cigar smoking with all-cause and cause-specific mortality and revealed that switching to pipe/cigar smoking is not a safe alternative for cigarette smokers to reduce the risk of cancer. Duration of smoking consumption was only associated with an increased risk of any cancer mortality, and lung cancer mortality. A longer duration of smoking cessation was associated with a decreased risk of all-cause mortality, and any cancer mortality. No associations were observed with prostate mortality or

breast cancer mortality. Therefore, our results indicate that the impact of lifetime cigarette and pipe/cigar smoking and duration of smoking varies for cause-specific mortality and sex. Finally, to determine which cause of death carried the highest risk we performed competing-risk analyses on mortality due to CVD, cancer, and other causes. The competing risk analyses showed that ex- and current smokers had a higher risk of both cancer mortality and CVD mortality compared to all other mortality causes. In addition, heavy smokers had a higher risk to die of cancer that to die of CVD.

Chapter 3 describes the association between cancer mortality risk and BMI measurements. Besides the poorly understood biological link between BMI levels and cancer incidence and mortality, the effect of lifetime changes in BMI on cancer mortality risk has scarcely been studied. The majority of previous studies were based on BMI measurements at only one time-point. Therefore we examined the association between BMI measurements at baseline, and lifetime changes in BMI (long-term and short-term) and cancer mortality risk in a large population-based cohort study. Additionally, we assessed whether the association between BMI and changes in BMI and cancer mortality risk is different for males and females. We found that being overweight at baseline was associated with a higher risk of prostate cancer mortality. Obesity at baseline was associated with a higher risk of any cancer mortality among all males and females combined, and within females alone as well. Chronically obese females (females who were obese during the entire follow-up period) had a higher risk of mortality from any cancer, lung cancer, colorectal cancer, and breast cancer. We found no significant association between long-term changes in BMI and cancer mortality risk. Both short-term BMI increase and short-term BMI decrease were associated with a lower mortality risk from any cancer among all subjects. Our study is the first to show that both short-term increase and short-term decrease in BMI were associated with lower mortality from any type of cancer.

Chapter 4 describes the impact of occupational exposures (gases/fumes, mineral dust, biological dust, all pesticides, herbicides, insecticides, and aromatic, chlorinated and other solvents, and heavy metals) and risk of mortality due to cancer. We found that high exposures to mineral dust and biological dust were associated with risk of mortality due to cancer. Occupational exposure to insecticides was associated with an increased risk of any cancer mortality. The observed significant associations were stronger for males compared to females and in ever smokers compared to never smokers. However, no significant interactions were observed between exposures and smoking or sex. There were no associations with exposure to gases/fumes, and herbicides. Some of our findings are in line with conclusions of recent other studies (3) and rendered new insight into the role of specific exposures in risk of cancer mortality. In addition, to our knowledge, this study is the first to investigate the potential role of smoking and sex in relation to different occupational exposures, including different subcategories of exposures, and overall cancer mortality.

Chapter 5 describes a genome-wide association study on all cancer mortality with the aim to identify novel cancer susceptibility loci. This study is limited to an initial GWAS on Caucasian individuals of Vlagtwedde-Vlaardingen, of which blood samples were obtained in 1989/90, and the vital status were assessed on December 31 2008 (18 years of follow-up). Among all 1546 included subjects, 141 had died due to cancer. The associations between SNPs, and cancer mortality risk were assessed using Cox proportional hazards regression under an additive genetic model with adjustment for age (continuous, at the final survey (1989/1990)), and sex, using the GenABEL package in R. In addition, we annotated SNPs to genes and investigated the gene functions. We also checked whether the top SNPs associated with cancer mortality were found in other GWA studies to be associated with other traits or diseases. Moreover, expression Quantitative Trait Locus (eQTL) mapping methods were used to identify whether SNPs were associated with gene expression (4). No SNP associations met the criterion of genome-wide significance ($P < 2.06 \times 10^{-7}$). However, we identified the 26 most significantly associated SNPs ($P < 1 \times 10^{-4}$) with any type of cancer mortality in *RCSD1, MSLN, NRXN1, PHIP, LRP1B, PHF21A,*

XKR5, NRXN1, CARD10, NBEA, EIF2AK3, and *MASP1* genes. The identification of new loci in this study may provide insight into the molecular mechanisms of cancer development. A next step would be to replicate our findings in other cohorts.

Chapter 6 describes the potential link between three objective allergy markers (number of peripheral blood eosinophil counts, skin test positivity and serum total IgE) and mortality and hospitalization from cancer. We investigated whether allergy is associated with cancer mortality and hospitalization after adjustment for potential confounders, in a general population sample in two Dutch communities (Vlagtwedde and Vlaardingen). We also assessed the possible effect modification of gender and smoking on the association between allergy and cancer since previous studies suggested these might have differential effects. Finally, to investigate the robustness of our results we conducted several sensitivity analyses. In the total population, no associations between objective allergy markers and cancer mortality or hospitalization were found, but several associations were found in specific subgroups. A higher number of eosinophils was associated with a decreased risk of colorectal cancer mortality in ever smokers and in males. Skin test positivity was associated with a decreased risk to die of any type of cancer in females. Serum total IgE levels were associated with an increased risk of lung cancer mortality among females, but with a decreased risk of cancer hospitalization in ever smokers and males. In conclusion, we found no associations between objective allergy markers and cancer in the total population. However skin test positivity and a high number of eosinophils were associated with a reduced risk to die of cancer in specific subgroups. Hence, it seems important to study specific subgroups defined by gender and smoking habits when studying the predictive value of allergy markers for cancer mortality.

Chapter 7 examines the association between serum uric acid levels (SUA) and mortality due to cancer among males. The link between SUA levels and cancer is complex, and current evidence is often contradictory and unclear. In addition, the role of SUA as independent risk factor for the development of cancer is controversial. Evidence shows there are positive associations between SUA and

established risk factors (such as body mass index (BMI), high levels of cholesterol, and triglyceride) for cardiovascular disease, metabolic syndrome, and cancer (5,6). Therefore, another objective of this chapter was to assess whether the association between SUA and cancer is independent of an individual's cholesterol and triglyceride levels. We found that higher levels of SUA were associated with a lower risk of mortality from any cancer. SUA levels in the highest tertile (> 5.8 mg/dl) were associated with a lower risk of mortality from any cancer. Additional adjustment for serum total cholesterol and triglyceride levels did not change the results. So far, the mechanism underlying the association between SUA and cancer is poorly understood. Therefore, more studies are needed to confirm our findings and to understand the mechanism by which uric acid affects the cancer mortality in both males and females.

General discussion

Risk factors for cancer mortality

Studies in this thesis described several environmental and genetic risk factors that may contribute to mortality of cancer. Therefore, our study helps to a better understanding of how several risk factors such as an individual's life style and genetic make-up contributes to mortality due to cancer in the general population. In addition, the risk factors described in this thesis are biologically plausible risk factors for future studies on cancer development and mortality.

Some studies described in this thesis aimed to confirm previously described associations between risk factors and cancer mortality. Replication of results from both longitudinal and cross-sectional studies is necessary to avoid uncritical acceptance of previous findings. Moreover, the histories of exposure to environmental risk factors have often been different across the different cohorts and populations (e.g., different cohorts often have different histories of tobacco smoke exposure) and they also may have different genetic predispositions. This suggests that findings in one population are not automatically generalizable to another population. Therefore, confirming findings from previous (cross-sectional) studies in

a well-defined cohort was one of the aims of the current thesis. For this aim we used longitudinal data, which is crucial for the investigation of lifetime risk factors for cancer mortality.

The Vlagtwedde-Vlaardingen cohort has unique data with over 40 years follow-up, which provides the possibility to investigate an individual's (changes in) lifetime risk factors for mortality due to cancer. In addition, information on major cancer risk factors such as age, smoking, BMI and occupational exposure was collected.

Tobacco smoking is currently the single largest preventable cause of cancer mortality worldwide (1). However, the link between tobacco smoking and some specific types of cancer such as colorectal, prostate, and breast cancer has not been reported consistently among the literature (7). A recent systematic review reported that although the pooled estimates show that cigarette smoking is associated with colorectal cancer incidence and mortality, there is significant heterogeneity across the studies (8). We found that moderate cigarette smoking and the number of pack years were associated with an increased risk of colorectal cancer mortality only among females. Similarly, Parajuli et al (9) suggested that females may be more susceptible to smoking-attributable colorectal cancer than males. The International Agency for Research on Cancer (IARC) Monograph on tobacco smoking in 2012 (7) reported that no conclusion on the association between smoking and prostate or breast cancer could be drawn. In line with this report, we found no association between smoking and prostate or breast cancer. Tobacco smoke is possibly linked to breast cancer risk through direct or indirect effects of carcinogens components of tobacco such as polycyclic hydrocarbons (PAH), aromatic amines and N-nitrosamines. Molecular investigations consistently show that the exposure to carcinogen components of tobacco may lead to a neoplastic transformation in breast tissue (10-13). However, results from epidemiological studies remain largely inconsistent. While the majority of studies reported no association, some studies suggested that this association if present is limited to pre-menopausal breast cancer and estrogen receptor positive breast cancer (10-13). These inconclusive results emphasize the importance of further investigations.

It has been proposed that many of the harmful effects of smoking are reversible in case of smoking cessation. However, the time that needs to pass before the risk of cause-specific mortality among ex-smokers reaches that of never smokers is less clear, and study outcomes remain largely inconsistent (14-16). Our findings indicate that smoking cessation was associated with a reduced risk of all-cause mortality, cancer mortality and CVD mortality compared to continuous smoking. Surprisingly, we found no association between smoking cessation and lung cancer mortality. So far, previous studies have shown inconsistent results for the association between smoking cessation and lung cancer. While the majority of studies showed a negative association, there are also some indications there is no association (17). The inconsistent results among studies may be partially explained by the fact that this association varies by histologic cell type. An increased duration of smoking cessation has been linked to a decreased risk of small cell and squamous cell carcinoma but not with adenocarcinoma (17,18). However, the mechanism underlying this association is unclear and warrants further studies.

Although there is compelling evidence that obesity is linked to cancer incidence of and mortality from some types of cancer such as breast, colorectal, pancreas, thyroid, and esophagus cancer, data on other types of cancer have shown mixed outcomes (19-21). Most importantly, like tobacco smoking, obesity may represent a potentially avoidable risk factor for cancer, and the attributable fraction of cancer mortality from obesity is also high (22). At the start of this project, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) released the major comprehensive, evidence-based report on the association between BMI and cancer, with recommendations for public health and personal goals for cancer prevention, with a continuous update process (CUP) (23). One of the most important factors for prevention of cancers mentioned in this report was maintaining a healthy weight throughout an individual's lifetime. Investigating the impact of lifetime long-term and short term changes in BMI on cancer mortality was one of the important themes in this thesis. We showed that a moderate to high short-term increase and a moderate to high short-term decrease in BMI are both associated with a decreased risk of mortality from any type of cancer, and mortality from breast cancer. Our

results are in accordance with those of a previous study by Michels et al. (24), that showed that both weight loss and weight gain are associated with decreased breast cancer incidence among premenopausal women. As indicated, we feel that these findings might be explained by the fact that the cause of the specific weight gain might be a protective factor for cancer, not the weight gain itself. In our study, for females, this short-term weight gain may be due to pregnancy, which is a protective factor for breast cancer. In smokers, short-term weight gain may be due to quitting smoking, which also decreases the risk of cancer. Further efforts need to be focused on understanding the processes linking obesity with cancer to develop new public health approaches to prevention and early detection of cancer in the at-risk overweight or obese population.

Within the studies presented in this thesis, occupational exposures to mineral and biological dust were among the most significant risk factors for mortality due to cancer in a general population. This emphasizes the importance of strategies to prevent and reduce occupational exposures. Although the potential links between occupational exposure and cancer risk are established, the majority of previous epidemiological studies were performed in specific subgroups, such as factory workers (25-27). Therefore, those findings may not be generalizable to the general population. Additionally, we addressed the interaction between occupational exposure and sex and occupational exposure and smoking on the risk of any cancer mortality, and found no significant interactions.

Currently, several methodologies exist for estimating occupational exposures and two Netherlands Cohort Studies (NLCSs) (28, 29) have discussed the reliability of these estimates for selected carcinogens. They have suggested that the DOM job-exposure matrix (JEM) might be a more appropriate way to determine carcinogenic exposures rather than using other matrixes such as the ALOHA+ JEM-based exposure estimates. This might suggest that the results of our current study should be interpreted with caution.

GWA Studies

GWAS is a hypothesis-free approach to identify genetic variations predisposing for different complex diseases including cancer. The advantage of GWAS is that there is no pre-selection of genes beforehand as in candidate gene studies and thus new loci associated with a disease or trait can be identified. It has been proposed that longitudinal data are advantageous for detecting genes that affect a trait or disease, because the longitudinal approach provides us with information on individuals during their lifespan, which is supposed to be more reliable than using information of just one single visit (30). Although a number of variants in association with cancer incidence have been identified, a limited number of GWAS on cancer mortality has been performed, and the majority of them addressed the survival among cancer patients rather than investigating cancer mortality in the general population. A recent systematic review of cancer GWAS and candidate gene meta-analyses summarized the findings from a decade of published genetic associations with cancer and reported some genes that were associated with the incidence of more than one cancer type. For instance, glutathione S-transferase mu 2 (muscle) (GSTM) gene has been reported to be associated with risk of bladder cancer, leukemia, lung cancer, and nasopharyngeal cancer incidence. So far, no GWAS or candidate gene study is available on overall cancer incidence or mortality in the general population. Our GWA study did not identify genome-wide significant SNPs ($P < 2.06 \times 10^{-7}$) with risk of any cancer mortality but we identified the 26 SNPs with a P-value $< 1 \times 10^{-4}$. The finding of this any cancer-associated SNPs extended the previous hypothesis that a single allele or locus mutation may lead to multiple phenotypes (pleiotropy) (4). Some examples of this hypothesis among previous studies are the variations in 8q24 (31), and 5p15.33 locus (32), which have been previously proposed to be associated with risk of several types of cancer. To get more clues about role of SNPs in cancer development, our findings need to be replicated in other cohorts.

Cancer and its association with objective allergy markers

The association between cancer and allergies has been a topic of interest for many epidemiological, oncological and immunological studies for several decades; however this association remains incompletely understood to date and results of previous studies are inconsistent. This type of discrepancy between results among studies is understandable, mainly because the association between allergies and cancer is complex and is based on both different types of cancer (33) and different definitions of allergy (34,35). Studies vary considerably in their definitions of allergy and allergy markers. For instance, very few studies distinguish between atopy (type-I allergy, IgE-mediated hypersensitivity) and allergy (immune hypersensitivity, regardless of the mechanism) (35). Results from chapter 6, corroborate the findings of previous work in this field; especially those who found no general association between allergy and cancer, with the same definition of allergy as we used (36-39), or based on a self-reported history of allergy (40).

Cancer and its association with SUA

SUA is the last breakdown product of purine metabolism in humans with controversial health consequences (41). Ames et al. (42), in 1982 for the first time hypothesized that SUA provides a primary defense against human cancer by its role as a scavenger of singlet oxygen, hydroxyl radical (a product of singlet oxygen conversion), and suppresses the lipid peroxidation in erythrocytes. So far, epidemiological studies investigating the association between SUA and cancer did not show results consistent with this hypothesis or with potential factors modifying this association (41,43). Evidence shows there are positive associations between SUA and established risk factors for cardiovascular disease, metabolic syndrome, and cancer, such as a high body mass index (BMI), and high levels of cholesterol or triglyceride. Thus, several confounding factors underlying these comorbidity disorders may explain a potential link between SUA levels and cancer (41,43). We studied the role of serum uric acid (SUA) as an antioxidant in cancer mortality. We were the first among epidemiological studies to show that SUA levels are associated with a lower risk of mortality from any type of cancer in males from a general

population cohort followed up for 38 years. This association remained after adjustment for serum total cholesterol and triglyceride levels. Nevertheless, we would recommend replicating the findings of our current study in independent cohorts as well as more immune-histochemical, molecular, and laboratory-based investigations to shed more light on the association between SUA and cancer mortality.

Future perspectives

Although the number of cancer survivors is growing, cancer is still the second causes of mortality worldwide (45-47). Therefore research on the potential risk factors underlying cancer mortality will remain a field of interest and will intensify in the future. Several epidemiologic studies have investigated the factors that affect the risk of cancer incidence, but only few have addressed the lifetime factors that may affect cancer mortality. In the current thesis, some of the findings were described for the first time, and therefore it is important to replicate these findings in other cohorts. Furthermore, investigation of the factors that affect other cancer outcomes, such as recurrence, risk of second malignant neoplasm, and the late effects of cancer treatments, beside the cancer incidence and mortality, may significantly contribute to decrease the burden of cancer (48).

This thesis showed several risk factors to be associated with risk of mortality due to any cancer and the four most common types of cancer. However, several issues remain to be solved by future studies. E.g. our study did not assess several other factors which may affect cancer development and mortality such as physical activity, alcohol consumption, and menopausal status of females. Moreover, the exact age of cancer diagnoses could not be determined in our cohort. Furthermore, candidate gene studies and analyzing gene-by-environment interactions might help to gain better understanding of the links between several potential risk factors and common types of cancer mortality.

Although the link between specific behavior and an increased risk of cancer is supposed to be well known to the general public, changing high risk behavior is

difficult for many individuals. Therefore, more research on the basic decision-making processes, and motivations to increase healthy behaviors are also needed to avoid cancer onset and improve cancer outcomes. Recently the National Cancer Institute (NCI) conducted a Questions Project (QP), which provides a novel funding for cancer epidemiologists (49). This project is an effort to identify unanswered scientific questions, categorized in five different cancer research areas, including cancer prevention and risk (50). One of the questions focuses on individual behavior, including addiction to tobacco use, and obesity-related behavior such as overeating and physical inactivity. Further investigations on the behavioral risk factors can help identify the best intervention strategies to eventually reduce the burden of cancer in the high risk populations.

In summary, cancer as a complex disease has several known environmental and genetic risk factors underlying it, but there probably also several risk factors that are still largely unknown. The meta-analyses of data from different cohorts, and advances in genetic studies including GWAS, will certainly contribute to a better understanding of the etiology of cancer in the long run.

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